

REMARKS

Claims 106 and 109-111 have been amended to replace "amino acids described" with "amino acid sequence set forth." Claims 107 and 122 have been amended to recite that the Xaa can be Cys, Ala, or Asn. Support for the amendment to claims 107 and 122 can be found, for example, at page 8, line 3 of the application. No new matter has been added. Applicants request reconsideration and allowance of claims 106-124, 127, 128, 131, 132, 135, 136, 139, 140, 151, 152, 155, 156, 159, and 160 in view of the above amendments and following remarks.

Applicants acknowledge that claims 125, 126, 129, 130, 133, 134, 137, 138, 141, 142, 145, 146, 149, 150, 153, 154, 157, 158, 161, and 162 are in condition for allowance and that claims 143, 144, 147, and 148 are objected to for being dependent upon a rejected base claim.

Objections

The Examiner objected to the amendment filed on August 31, 2007, for containing new matter with respect to the recitation of "Xaa" in SEQ ID NO:38. Applicants have amended claims 107 and 122 to refer to asparagine, i.e., Asn. The Examiner is requested to withdraw the objection to the amendment.

Rejection under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 106-120 under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner asserted that the phrase "no more than 29 amino acids . . . which are different from the amino acids described in SEQ ID NO:38" was confusing as it was unclear whether the comparison was based on amino acid composition or amino acid sequence.

Applicants have amended claim 106 to recite that the variant form has no more than 29 amino acids other than position 214 of SEQ ID NO:38 which are different from the amino acid sequence set forth in SEQ ID NO:38. Claims 109-111 also have been amended in a similar manner. Claims 106-120 are sufficiently definite under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 107 and 122 under 35 U.S.C. 112, first paragraph, for lack of written description. The Examiner asserted that the recitation of "Asp" with respect to position 214 of SEQ ID NO:38 was new matter.

Claims 107 and 122 have been amended to recite that Xaa is selected from the group consisting of Cys, Ala and Asn. Support for the amendment can be found, for example, at page 8, line 3 of the application. The Examiner is requested to withdraw the rejection of claims 107 and 122 under 35 U.S.C. §112, first paragraph.

Double-Patenting

The Examiner provisionally rejected claims 106-107, 109, 112-115, 118-120, 127, 131, 135, 139, 151, 155, and 159 under the judicially created doctrine of double patenting over claims 1-4, 6-10, 14-16, 18-19, 21, and 35-37 of co-pending Application No. 10/111,723.

Applicants request that the rejection be held in abeyance until the application is in condition for allowance.

Rejection under 35 U.S.C. §103

The Examiner rejected claims 106-108, 112-115, 118-123, 127, 131, 135, 139, 151, 155, and 159 under 35 U.S.C. §103 as being obvious over Thompson et al. (J. Biol. Chem. 272:18766-18771, 1997; "Thompson U") in view of Thompson et al. (Gene 103:171-177, 1991; "Thompson V"), Hirokawa et al. (U.S. Patent No. 6,074,859; "Hirokawa") and Lowe et al. (U.S. Patent No. 6,132,983; "Lowe").

The Examiner rejected claims 109, 124, 128, 132, 136, 140, 152, 156, and 160 under 35 U.S.C. §103 as being obvious over Thompson U in view of Hirokawa and Lowe as applied to claims 106-108, 112-115, 118-123, 127, 131, 135, 139, 151, 155, and 159 and further in view of additional teachings of Thompson U and Lowe.

Applicants disagree with the Examiner.

Thompson U observed that regions 206-220 and 329-341 of *P. pyralis* luciferase were sensitive to proteolysis and mutagenized the region around residue 200. It was found that many highly conserved residues, including residues 198, 201, 202, and 203, could be mutagenized and retain luminescent activity. However, substituting an alanine residue for serine at position 199 or substituting an alanine for glycine at position 200 resulted in a complete loss of activity. See Thompson U at page 18767. Thompson U also reports that others have found that changes at position 206 were detrimental to luciferase activity. See Thompson U at page 18770. Thompson U does not direct one of ordinary skill in the art to make a mutation at position 214.

Thompson V indicates that luciferase is unstable and that competitive inhibitors can be used to increase its stability. Lowe indicates that *P. pyralis* luciferases having a substitution at position 215 or 354 have increased heat stability over wild-type *P. pyralis* luciferase. Hirokawa indicates that *P. pyralis* luciferase having a substitution at position 217 has increased heat stability over wild-type *P. pyralis* luciferase. The Thompson V, Lowe, and Hirokawa references do not direct one of ordinary skill in the art to make a mutation at position 214.

The Examiner acknowledges that the art is silent with regards to the effects of mutating *P. pyralis* luciferase at position 214 at pages 10 and 13 of the office action yet asserts it would have been obvious to combine the teachings of Thompson U, Lowe, or Hirokawa to mutate wild-type *P. pyralis* luciferase at position 214 alone or in combination with a mutation at position 354. The Examiner alleged one of ordinary skill would have been motivated to do so because "Thompson U specifically identifies amino acids 206-220 as a region for mutation and teaches replacing amino acids within this region with alanine; Thompson U, Lowe, and Hirokawa each demonstrate that amino acid mutation within this region products mutant *P. pyralis* luciferase polypeptides with improved stability relative to wild-type *P. pyralis* ; and the use of a stabilized mutant luciferase would increase half-life and stability without requiring luciferin analogs." The Examiner cited to MPEP §2112 and further asserted that *P. pyralis* with a mutation at position 214 alone or in combination with a mutation at position 354 would necessarily have luciferase activity and increased thermostability as compared to wild-type *P. pyralis* luciferase. Applicants disagree.

As indicated in MPEP §2112, the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted).

Based on the cited references, it is not inherent that a *P. pyralis* mutant containing a mutation at position 214 would have activity or increased thermostability. None of the references made a mutation at this position. Thompson U establishes that mutations at adjacent or nearby residues can produce different results in a mutated protein. For example, *P. pyralis* luciferases having changes at amino acids 198, 201, 202, or 203 retained 10-100% of wild-type luminescent activity. See page 18767 of Thompson U. By the Examiner's rationale set forth in the office action on pages 10 and 13, it would be expected that luciferase containing a change at position 199 or 200 also would retain luminescent activity. However, changes at amino acids 199 or 200 resulted in a complete loss of activity. See page 18767 of Thompson U. Thus, the Examiner's rationale is misguided. In view of the above, one of ordinary skill in the art would not recognize the claimed subject matter to be inherent in the combination of cited references. The Examiner is requested to withdraw the rejection of claims 106-109, 112-115, 118-124, 127, 128, 131, 132, 135, 136, 139, '40, 151, 152, 155, 156, 159, and 160 under 35 U.S.C. §103.

CONCLUSION

Applicants submit that claims 106-162 are in condition for allowance, which action is requested. The Examiner is invited to call the undersigned agent at the telephone number below if such will advance prosecution of this application.

Please apply \$460 for the Petition for Extension of Time fee and any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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